REMARKS

GENERAL COMMENTS

The Office Action of March 6, 2006 has several rejections, each of which are responded to individually below.

Claims 149-188 are pending in the application.

Claim 149 is amended herewith only for the purpose of clarity and grammatical correctness. The amendment to claim 149 is not in response to any of Examiner's rejections. Therefore, the amendment should not be interpreted in any manner as surrendering subject matter for the purpose of achieving allowance of the claimed subject matter.

Claim 155 has been amended in accordance with the rejection under §112, 2nd paragraph, for lack of antecedent basis for "the antigen."

New claims 189-192 are added with this amendment. Newly added claims 189-192 are adequately supported by the specification and do not introduce any new matter.

For example, Figure 1 dramatically illustrates the mutual enhancement provided by the β-glucan and an antibody. When administered individually, neither the β-glucan nor the antibody, effectively inhibit tumor growth. However, in conjunction, the combination of β-glucan and antibody effectively inhibits tumor growth *in vivo*. In addition, the 1,3 linkages of the β-glucan are disclosed throughout the application, as is the glucan being combined with antibodies.

DOUBLE PATENTING

The provisional statutory double patenting rejections are acknowledged. Applicant respectfully requests that the provisional rejections be held in abeyance until one set of the allegedly conflicting claims is allowed.

REJECTIONS UNDER § 103(A)

Examiner has rejected claims 149-160, 163-184, 186 and 188 for allegedly being obvious over the combined teachings disclosed in the cited works of Herlyn, James [sic], Yan et al., Marciani, Cheever, Chu and Lane. Applicant respectfully disagrees with the Examiner's interpretation of these references and their application to supporting a nonobvious rejection under § 103(a) to the pending claims.

As set forth in MPEP § 706.02(j)(Contents of a 35 U.S.C. 103 Rejection):

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143 - § 2143.03 for decisions pertinent to each of these criteria.

In accordance with these PTO guidelines, it is respectfully suggested that the references are not properly combined. Further, for the sake

of argument, even if the references are combined, they fail to teach or suggest each limitation of the pending claims.

Examiner states that "Herlyn teaches a method of treating human tumors *in vivo* by providing a 1,3 backboned glucan followed by treatment with anti-tumor monoclonal antibodies." Applicant strongly disagrees. Neither Herlyn, nor the other references provide any teachings or guidance that would lead persons of ordinary skill in the art to a composition comprising an (1) orally administered β-glucan composition, and (2) that effectively inhibits tumor growth *in vivo*.

Applicant's claims are directed to compositions and their methods of use for an *in vivo* combination approach to cancer treatment. Specifically, the composition of β-glucan is orally administered to a subject in order to enhance the efficacy of the anti-cancer antibody, which is also administered *in vivo*. Herlyn does not teach the claimed composition. Herlyn teaches the intraperitoneal injection of a β-glucan in mice, but does not teach or suggest that oral administration of β-glucan is an effective alternative. She further teaches that activated macrophages may be removed from the injected mice and incubated *in vitro* with tumor cell lines and an anti-tumor antibody. Following these steps, Herlyn merely demonstrates an enhanced percentage of the *in vitro* lysis of cultured tumor cells when compared to the extent of lysis when non-activated macrophages (i.e.,no β-glucan injection) are incubated *in vitro* with the same antibody.

Thus, it is respectfully brought to Examiner's attention that his interpretation of Herlyn's teachings as stated on page 4 of the office action, paragraph B, is not correct. Examiner states that

Herlyn treats mice with β-glucan "followed by treatment with anti-tumor monoclonal antibodies. See abstract." Although such language appears in the abstract, there is no such antibody treatment of a tumor or cancer disclosed.

Herlyn does not teach or suggest the much preferred noninvasive oral route of administering β-glucan. Nor does Herlyn treat any cancer *in vivo*. In fact, the mice receiving the intraperitoneal β-glucan never had a tumor, or even a single cancer cell of any kind, growing in it. Tumor cell lines and antibodies were added to activated macrophages *in vitro*.

In conclusion:

- Herlyn does not teach or suggest an *in vivo* combination cancer therapy in which orally administered β-glucan enhances the *in vivo* effectiveness of an anti-tumor antibody;
- Herlyn does not teach or suggest the efficacy of a noninvasive oral β-glucan preparation orally;
- Neither does Herlyn disclose the effectiveness of her "method" *in vivo* with tumor-bearing mice.

Thus, Herlyn's disclosure taken individually, or in combination with the other cited references cannot reasonably be interpreted as teaching or suggesting a composition that shrinks the size or inhibits the growth of, a growing cancer in a living organism.

It is further respectfully suggested that the additional cited references cannot cure the deficiencies of Herlyn's disclosure.

Specifically, US '720 to Jamas et al., teaches the intravenous and subcutaneous administration of β-Glucan as a technique to activate leukocytes' general defense mechanisms (e.g., phagocytosis and sepsis). See Examples 4-6 in Jamas. Thus, the disclosure of US '720 does not extend the relevant teachings of Herlyn. On the contrary, they are significantly more narrow because Jamas,

- does not teach or suggest an *in vivo* combination cancer therapy of orally administered β-glucan to enhance the effectiveness of an anti-tumor antibody;
- does not teach or suggest oral administration of a β-glucan;
- does not provide any conceptual or practical guidance related to combining anti-tumor antibodies with β-glucan; and
- does not actually examine the effects of glucan in conjunction with antibodies on tumor cells either *in vitro* or *in vivo*.

Applicant respectfully suggests that persons of ordinary skill in the art could not combine Herlyn with the teachings of Jamas and arrive at the claimed composition.

In sum, the combined teachings of Herlyn and Jamas do not reach a *prima facie* case of obviousness. As discussed below, their combined teachings and disclosures cannot be remedied by the additional cited references.

For example, Yan et al, also does not teach or suggest the claimed subject matter. Yan only discloses the invasive method of intraperitoneal and intravenous administration of β-glucan. There is no disclosure relating to oral β-glucan administration. Further, the text that Examiner cites in Yan relates to the *in vitro* use of an

anti-GD2 monoclonal antibody in ADMC assays. Therefore, the foregoing discussion of the inadequacies in Herlyn and Jamas, applies with equal force to Yan et al.

The Chu, Cheever and Lane references do not, individually or in combination disclose the use of β-glucan in anti-cancer or anti-tumor treatment, let alone its effective oral administration. These references are apparently cited to indicate that certain antigens and antibodies are known in the art. However, persons of ordinary skill in the art would not, and could not combine the teachings of Chu, Cheever and Lane with those of Herlyn, Jamas and Yan and arrive at the claimed subject matter.

The combined teachings of these references do not support Examiner's conclusion that persons of ordinary skill in the art could rely upon them and have a reasonable expectation of success at arriving at an effective anti-cancer composition comprising:

- an orally administered β-glucan,
- an anti-tumor antibody, wherein
- the β-glucan and antibody mutually enhance the other's anti-tumor efficacy *in vivo* and
- effectively demonstrate an *in vivo* growth inhibition of tumor and cancer cells.

In accordance, it is respectfully suggested that the rejection under § 103(a) should be withdrawn. The combined references do not teach or suggest the claimed subject matter to an extent permitting persons of ordinary skill in the art to proceed toward the claimed composition with a reasonable expectation of success. As stated above, the references taken in combination do not teach or suggest every claim limitation in independent claim 149.

In accordance, withdrawal of the rejection under § 103(a) is earnestly requested.

REJECTIONS UNDER § 112, 1ST PARAGRAPH

Claims 149-188 were rejected under § 112, 1st paragraph, because Examiner believes that the claims do not enable "all types of cancers and antibodies generally." Further, Examiner states that "administering an effective amount of beta glucan and specific monoclonal antibody, 3F8," does not reasonably provide enablement for all types of cancers and antibodies generally.

Examiner supports his position by reference to the well-known difficulties that have arisen in treating various cancers that are caused by a multitude of external influences, e.g., virus, environmental insult, tobacco, radiation, and a person's genetic predisposition. Put succinctly, Examiner believes that in view of the multitude of cancer types and causes there can never be a "silver bullet" for treating cancers generally. Examiner concludes that the pending claims are overly broad in scope.

Examiner's Burden

In response, Examiner is respectfully reminded that in order to make a nonenablement rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). MPEP § 2164.04

Examiner's stated rationale for asserting that the claims are not enabled by the specification would be appropriate if the subject matter disclosed and claimed were merely a modification or continuation of the same technological approaches. However, this is not the case at hand. It is respectfully suggested that Examiner's rationale indicates that he has not adequately considered the groundbreaking technology described and claimed herein. That Applicant's invention is, indeed, worthy of being referred to as groundbreaking can be instantly appreciated by the absence of prior art encompassing the claimed subject matter.

Biological versus Pharmacological Approach

Examiner's reiteration of the difficulties in treating cancers is based on the history of pharmacological approaches of identifying cytotoxic compounds that specifically destroy cancer cells. The intracellular targets of these small cytotoxic pharmaceuticals are components involved in cell replication because this process is carried out in tumor cells with greater frequency than most normal cells.

The obvious problem has been that these small molecule cytotoxic compounds cannot specifically target tumor cells; they also accumulate in normal cells. Further, because the molecular composition of cancer cells and normal cells is very similar, the accumulated cytotoxic compounds also exert their adverse effects on normal cells, thereby, causing serious side effects.

The nonspecific targeting of radiation also adversely affects normal cells. Thus, radiation treatment possesses similar drawbacks to those encountered with administering cytotoxic compounds.

In contrast, Applicant's focus on synergistically enhancing the efficacy of administered specific anti-tumor antibodies *in vivo* greatly alters the conceptual landscape of treating cancers. A key element of this conceptual approach, is a change of focus from seeking to specifically and chemically target cancer cells, to specifically and biologically targeting them. This has been achieved by taking advantage of the specificity offered by an anti-tumor antibody (i.e., does not target normal cells) and synergistically enhancing the antibody's effect by non-invasively and orally administering β-glucan.

The claimed composition provides a potent means to inhibit tumor growth across a broad spectrum of tumors. The Applicant's specification provides the necessary guidance to persons of ordinary skill in the art on the critical variables and their modification, should it be necessary. Further, in contrast to Examiner's comments, the instant application discloses results for five distinct antibodies, not only 3F8. This indicates that the claimed subject matter is likely to have far broader utility than what had preceded it, and accordingly, it should be reflected in the scope of the claims. See published application, para [0099] to [0100], and the table on p. 7.

Applicant's Claims are Enabled by the Specification

A. *Persons Of Ordinary Skill In The Art Would Not Require Undue Experimentation to Practice the Claimed Subject Matter*

A claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. In re Certain Limited-Charge Cell Culture Microcarriers, 221 USPQ 1165, 1174 (Int'l Trade Comm"n 1983), *aff'd. sub nom.*, Massachusetts Institute of Technology v. A.B. Fortia, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). MPEP § 2164.01.

In the present case, it is respectfully suggested that any experimentation involved in using the claimed composition is neither undue, nor is it complex. A characterized putative monoclonal anti-tumor antibody would be administered with the glucan and tested for its efficacy. All procedures are well-known, e.g., hybridoma technology, characterizing the specificity of antibody binding, and analyzing tumor growth. It is respectfully suggested that any experimentation required to make and use the claimed composition is clearly not undue and not even complex. Thus, it is inaccurate to conclude that the claimed subject matter is not enabled under § 112, 1st paragraph.

It is respectfully noted that there is no reasoning or evidence provided by Examiner to indicate that it is more likely than not that the claimed composition comprising any complement-fixing anti-tumor antibody would not be effective. Assuming, *arguendo*, that Examiner believes that the claims encompass inoperative embodiments, that by itself is not sufficient to render the claim nonenabled. As set forth in MPEP § 2164.08(b):

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort

than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling).

It is respectfully suggested that Examiner has not set out any basis for believing that persons of ordinary skill in the art would not be reasonably appraised of the kinds of antibody and glucans to employ in any given embodiment of the claimed composition. Absent such reasoning or evidence, it would be improper to maintain the instant rejection.

It is respectfully requested that the rejection based on the claims' alleged lack of enablement be withdrawn.

B. Current Activity Of Persons Of Ordinary Skill In The Art

The research activity in the field of glucan-enhanced immunotherapy published after Applicant's priority date provides substantial evidence that Applicant's specification enables the full scope of the claims. Further, cautions or discussion of inoperative embodiments has not yet surfaced.

In Allendorf, et al.,((2005) The Journal of Immunology, 174; 7050-7056), a copy of which is submitted herewith as **Exhibit A**, the role of granulocytes in the oral β-glucan-enhanced monoclonal antibody anti-tumor activity was demonstrated. Applicant's contributions were cited several times. More significant is that soluble and particulate glucan were both effective. Further, two additional monoclonal antibodies, one to a ganglioside and one to mammary adenocarcinoma, were effectively combined with the β-glucan.

A review article, attached herewith as **Exhibit B**, by Gelderman et al., ((March, 2004)TRENDS in Immunology 25;158-164, provides a review of the role of the complement system in immunotherapy. One focus of the article is how tumor cells become coated with proteins that actually regulate the complement system's ability to target them during conventional monoclonal antibody-based therapy. On page 162 of the article the authors describe efforts to employ glucan adjuvant therapy to overcome the protection of tumor cells by complement regulatory proteins. The second paragraph of column 2 states:

> Initial reports showed this adjuvant activity with intravenously administered soluble yeast β-glucan , however, it now appears probable that certain large molecular size β-glucans can have this same complement-dependent adjuvant function when given orally. This is an advantage when being clinically administered. Cheung et al. showed that large molecules of barley b-glucan given orally to mice functioned as adjuvants that ***greatly promoted*** the tumor regression activity of mAbs that activated complement. Moreover, studies with mouse tumor models showed that ***oral b-glucan therapy could greatly augment*** tumor regression mediated by anti-CD20, anti-HER2/neu and anti-EGFR1 . The combined use of oral or intravenous β-glucans with mAb therapy recruits granuloytes as tumor killer cells. The current data suggest that orally administered β-glucan functions through anti- tumor mAbs and the complement system to recruit CR3þ effector cells that produce tumor regression and tumor- free survival.

[Emphasis added]. Thus, the authors cite Applicant, and express a very high expectation of the effectiveness of Applicant's approach, even in modified versions.

Hong et al., ((2004), Journal Immunology, 173 ;797-806)), attached herewith as Exhibit C, employed Applicant's teachings to effectively reduce tumor growth *in vivo* of a both a lymphoma and a Lewis Lung carcinoma. The authors reported that bone marrow granulocytes bound β-glucan fragments

> "Orally administered β-1,3-glucans were taken up by macrophages that transported them to spleen, lymph nodes, and bone marrow. Within the bone marrow...β-1,3-glucan fragments that were taken up by the CR3 [receptors] of marginated granulocytes [white blood cells formed in the bone marrow]. These granulocytes with CR3-bound B-1,3-glucan-fluorescein were shown to kill iC3b-opsonized tumor cells following their recruitment to a site of complement activation **resembling a tumor coated with mAB** [monoclonal antibodies]."

[Emphasis added]. Thus, using different antibodies and tumors, the authors demonstrate that Applicant's specification was clearly enabling to expand the scope of effective treatments.

Yan J, et al., have extended Applicant's work to employing particulate glucan from yeast. In their recent review article (Expert Opin Biol Ther; 5(5):691-702), attached herewith as **Exhibit D** they state that "***[e]xtensive*** studies in preclinical animal tumour models have demonstrated the efficacy of combined oral particulate yeast beta-glucan with antitumour mAb [monoclonal antibodies] in terms of tumour regression and long-term survival. It is proposed that the addition of beta-glucan will further improve the clinical therapeutic efficacy of antitumour mAbs in cancer patients." [Emphasis added].

It is respectfully suggested that the authors' beliefs that the methodology has undergone extensive experimentation, together with their positive outlook toward improving tumor immunotherapy further establishes that Applicant's claims are supported by an enabling specification. If, as Examiner believes, undue experimentation were required to practice the claimed invention, it is unlikely that so large a flurry of activity after Applicant's priority date would have been found. Further, it should be pointed out that this activity is directed to employing different β-glucans, e.g., particulate, and different monoclonal antibodies. Thus, it is clear that persons of

ordinary skill in the art were able to modify the claimed compositions and methods to suit their own interests.

The widespread popularity of coupling noninvasive oral β-glucan administration with immunotherapy can also be found discussed on websited devoted to advances in β-glucan uses in medical treatments. See, e.g., http://www.beta-glucan-info.com/cancer_study.htm, entitled *Beta Glucan and Monoclonal Antibody Study Results*, attached herewith as **Exhibit E**.

In conclusion, there has been substantial activity in the field of oral-glucan enhancement of immunotherapy after Applicant's pioneer work. The work described above falls within the scope of utility of Applicant's invention. Clearly, by using Applicant's teachings persons of ordinary skill in the art have effectively implemented additional monoclonal antibodies and therefore additional cancers, as well as various types of the β-glucans that may be used.

It is noteworthy that failures in attaining an efficacious anti-tumor protocol based on Applicant's specification oral β-glucan enhancing anti-tumor antibody cell killing have not yet been identified. Neither have serious limitations been placed on the applicability of the claimed subject matter.

Therefore, it is respectfully requested that Examiner reconsider the extent of enablement afforded Applicant's specification. The recent studies described above provides strong evidence that persons of ordinary skill in the art are fully able to effectively practice and modify the claimed subject matter without undue experimentation.

Accordingly, withdrawal of the rejection is earnestly solicited.

§ 112, 2nd paragraph

Claim 155 was rejected for lacking antecedent basis for the term "the antigen." In response, this claim is amended herewith and is believed to overcome this rejection.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, above that required for the three month extension and the additional fee for the additional claims, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891.

Respectfully submitted,

I hereby certify that this paper is being deposited this date with the U.S. Postal Service with sufficient postage for first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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